Pergamon

Tetrahedron Letters 43 (2002) 569–572

TETRAHEDRON
LETTERS

Synthesis and oxidation reactions of a user- and eco-friendly hypervalent iodine reagent

Arun P. Thottumkara[a] and Thottumkara K. Vinod[b,*]

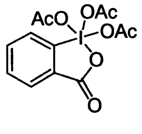
[a]*Macomb High School, Macomb, IL 61455, USA*
[b]*Department of Chemistry, Western Illinois University, Macomb, IL 61455, USA*

Received 15 September 2001; revised 19 November 2001; accepted 20 November 2001

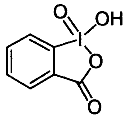
Abstract—Allylic and benzylic alcohols are cleanly oxidized to the corresponding carbonyl compounds in water or water–THF mixtures using a water-soluble derivative of *o*-iodoxybenzoic acid. A mechanism involving single electron transfer steps is proposed for this facile and eco-friendly oxidation protocol. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Hypervalent iodine reagents, due to their low toxicity and ready availability, have attracted considerable attention recently as mild and selective oxidizing agents.[1] Of the various hypervalent iodine reagents known, Dess–Martin periodinane (DMP), **1**,[2] and *o*-iodoxybenzoic acid (IBX), **2**,[3] are the most commonly used. Despite the nontoxic nature of these compounds and their ease of preparation, these reagents have certain drawbacks. Both reagents are potentially explosive and, thus, cannot be stocked in large quantities. In addition to this drawback, oxidation of alcohols using DMP are carried out in environmentally unsafe chlorinated solvents and reactions employing IBX are often limited in dimethyl sulfoxide (DMSO) due to the reagent's insolubility in other common organic solvents. While oxidation reactions using both DMP and IBX tolerate the presence of moisture in the reaction medium,[1f,2c] the presence of large amounts of water, when used as a solvent or co-solvent, is detrimental to the outcome of the oxidation reactions using these reagents. This is due to the fact that the mechanisms of oxidation with both the oxidizing agents involve reactive intermediates formed in an equilibrium step that is disfavored with increasing concentrations of water.[1f,g]



1



2

3

A series of elegant papers from Nicolaou Laboratories have recently identified several new oxidative transformations, including a selective oxidation of benzylic carbons using IBX.[4] These reactions were carried out either in DMSO or fluorobenzene/DMSO mixtures. Single electron transfer (SET) reaction pathways have been proposed for these synthetic technologies.[4c,d,f] A significant aspect of the new oxidative transformations that caught our attention is that the presence of water does not affect the outcome of these reactions. The ever-growing demand for eco-conscious chemical processes[5] and our interest in green-chemistry prompted us to synthesize a water-soluble derivative of IBX that could potentially behave as a *green-oxidant* capable of oxidizing alcohols in water, possibly via a SET mechanism (vide infra), similar to the one proposed by Nicolaou. In this paper we describe the synthesis of **3**, a water-soluble derivative of IBX, which we call modified IBX (mIBX), and oxidation of allylic and benzylic alcohols using **3** in water and other eco-friendly solvents.

2. Results and discussion

2.1. Synthesis of mIBX

The synthesis of mIBX, **3**, is readily accomplished from commercially available 3-nitrophthalic acid (**4**) as follows: esterification of **4** via the corresponding acid chloride gave nitrodiester, **5** (100%), which upon catalytic hydrogenation provided the aminodiester, **6**

Keywords: hypervalent iodine reagent; oxidation; green-oxidant; single electron transfer.

* Corresponding author. Tel.: 309-298-1379; fax: 309-298-2180; e-mail: mftkv@wiu.edu

PII: S0040-4039(01)02217-1

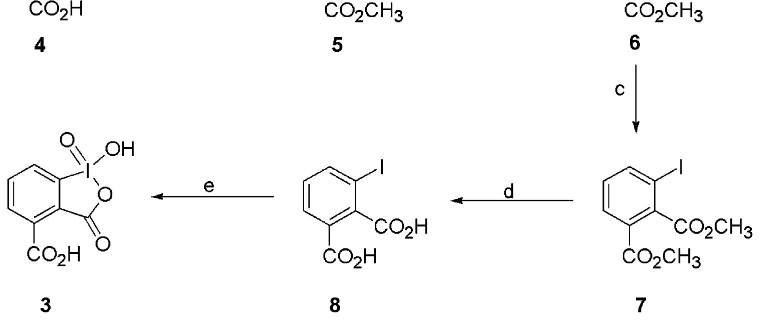
(100%). Diazotization followed by iodination of **6** provided dimethyl 3-iodophthalate (**7**) in 91% yield. Saponification followed by acidification of **7** yielded 3-iodophthalic acid (**8**) in 93% yield. Oxidation of **8** to the water-soluble mIBX, **3**, was carried out using $KBrO_3$[6a] (Scheme 1). The 70% yield reported for the conversion of **8** to **3** is the isolated yield of **3**, with the actual conversion near quantitative as evident from monitoring the oxidation of **8** to **3** by ^1H NMR spectroscopy. Water-soluble mIBX, **3**, was isolated as an analytically pure white solid, mp: 258–260°C.[6b,c]

2.2. Oxidation of alcohols with mIBX

With mIBX at hand, we decided to investigate its use as a *green-oxidant* by initially monitoring the oxidation of benzyl alcohol, 2-hexenol, 2-phenylethanol and cyclohexanol using ^1H NMR and using D_2O as the solvent. The selective oxidation of allylic and benzylic alcohols from this short list of substrates prompted us to investigate the oxidation of a series of allylic and benzylic alcohols to establish the limitations of the new reagent in terms of its selectivity and compatibility with other functional groups, and the results are summarized in Table 1. Tetrahydrofuran (THF) was used as co-solvent when necessary without impeding the effectiveness of the reagent. As evident from Table 1, mIBX efficiently oxidizes a variety of allylic and benzylic alcohols and tolerates the presence of a series of functional groups during the oxidation. Over-oxidation products are never observed, even when electron rich substitutents are present on the ring (entry 7). Monitoring the progress of the oxidation of 1,2-benzenedimethanol (entry 8) indicated that the presence of the electron withdrawing formyl group (formed in the course of the oxidation) did not adversely affect the rate or the yield of the final dialdehyde product. Oxidation of the same substrate using IBX in DMSO gave the corresponding lactol as the product, clearly delineating the difference in the mechanism of oxidation using the two structurally analogous reagents in two different solvents.[7] Presence of electron withdrawing groups also does not affect the rate or the yield of the final product (entries 5 and 9). Oxidation of vicinal diols occurs without accompanied oxidative cleavage (entries 10 and 11). Oxidation of 1-phenyl-1,2-ethanediol (entry 11) gave 55–60% isolated yield of 2-hydroxyacetophenone indicating the selectivity of mIBX towards benzylic OH groups. This particular oxidation carried out with a 1:1 substrate to mIBX ratio also gave 20–25% yield of benzoylformic acid, an apparent over-oxidation product! Formation of benzoylformic acid via an enol and a subsequent ketene intermediate generated from the initially formed benzylic radical will be described in a detailed manuscript. The selectivity of mIBX towards benzylic OH groups is also noted in the oxidation of non-vicinal diol (entry 12) to the corresponding benzaldehyde.

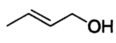
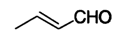
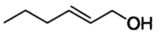
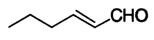
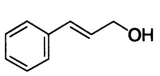
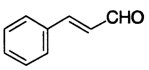
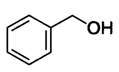
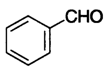
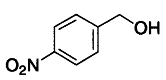
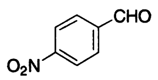
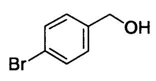
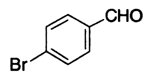
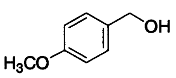
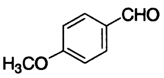
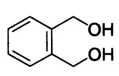
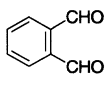
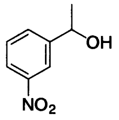
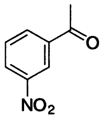
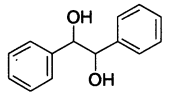
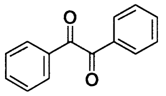
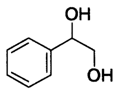
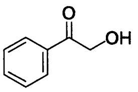
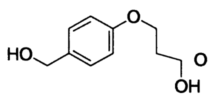
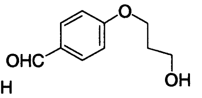
Based on our results and the inability of mIBX to oxidize non-allylic/benzylic alcohols, we propose the following plausible mechanism (Scheme 2) for the oxidation of allylic and benzylic alcohols. The salient features of this mechanism include the α-H abstraction from benzyl alcohol by mIBX to give **9** (mIBX radical) and **10**, a benzylic radical. A subsequent SET from **10** to **9** generates the carbocation **13** which then gives benzaldehyde as shown in Scheme 2. An important aspect of this oxidation protocol is the nearly complete insolubility of **12**,[9] the reduced form of mIBX, in water which allows for easy removal of the spent reagent by filtration. The work-up of oxidation reactions carried out in water using mIBX thus involves only filtration and a subsequent removal of the solvent.[8] An easy re-oxidation of **12** to **3** using $KBrO_3$ makes the procedure cost-effective, as well.

In summary, we have synthesized an user- and eco-friendly hypervalent iodine reagent capable of selectively oxidizing allylic and benzylic alcohols in water and other eco-friendly solvents. The oxidation protocol using this chemoselective reagent is operationally simple, providing good to excellent yields of the carbonyl compounds.



Scheme 1. *Reagents and conditions*: (a) (i) $SOCl_2$, heat, (ii) CH_3OH, heat, 100%; (b) H_2 (55 psi), Pd-C, CH_3OH, 100%; (c) (i) $NaNO_2$, HCl, 0–5°C, (ii) KI, 91%; (d) (i) NaOH, THF–H_2O (3:1v/v), (ii) aq. HCl, 93%; (e) $KBrO_3$, 0.73 M H_2SO_4, 55°C, 3 h, 70%.

Table 1. Oxidation of allylic and benzylic alcohols using mIBX

Entry	Substrate	Product	Conditions[a]	% Yield
1	 *cis-trans* mixture	 *cis-trans* mixture	1:2, H_2O, RT, 18 h	86[b]
2			1:2, H_2O, RT, 18 h	90[b]
3			1:2, H_2O, RT, 18 h	90
4			1:1.5, H_2O, 60^0C, 3 h	95
5			1:1.5, H_2O:THF (5:2 v/v)[c] 60^0C, 3 h	79
6			1:1.5, H_2O:THF (5:2 v/v)[c] 60^0C, 3 h	89
7			1:1.5, H_2O, 60^0C, 3 h	95
8			1:2.5, H_2O, 60^0C, 3 h	80
9			1:1.5, H_2O:THF (4:3 v/v)[c] 60^0C, 3 h	96
10			1:2.5, H_2O:THF (3:3 v/v)[c] 60^0C, 3 h	81
11			1:1, H_2O, 60^0C, 3 h	60[d]
12			1:2 H_2O, 60^0C, 3 h	94

---

[a] Reaction conditions are noted in the following order: Substrate to mIBX ratio, solvent(s), temperature, time

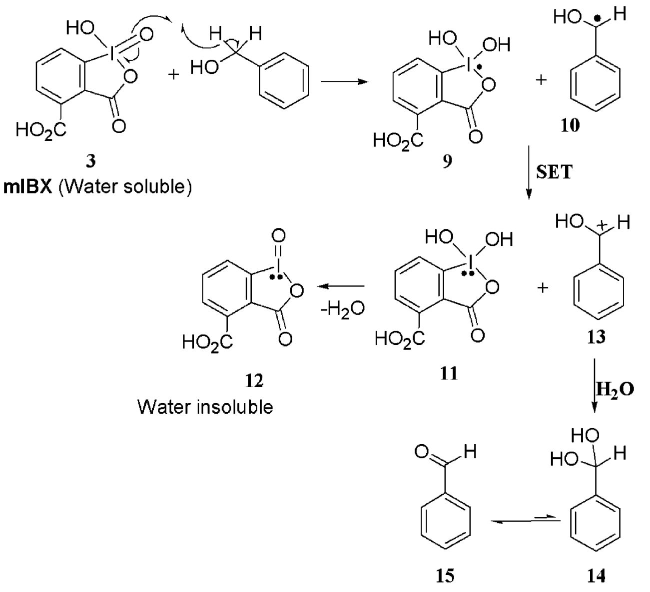
[b] The yield reported for entries 1 and 2 are calculated using gas chromatography. The other yields reported in Table 1 are isolated yields.

[c] Formation of γ-butyrolactone (~10%), via oxidation of THF, was observed from reactions carried out in the mixed solvent system.

[d] Nearly 25% of phenylglyoxalic acid was also isolated from this reaction.

Acknowledgements

Financial support for this work by the University Research Council of Western Illinois University is gratefully acknowledged. We also gratefully acknowledge the support of the National Science Foundation (ILI grant no. DUE-9851569) and Western Illinois University for funding the NMR spectrometer used in this study.



Scheme 2. Mechanism of oxidation of benzylic/allylic alcohols in water using mIBX.

References

1. (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997; (b) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Intl. Ed.* **2000**, *39*, 1306–1308; (c) Togo, H.; Nabana, T.; Yamaguchi, K. *J. Org. Chem.* **2000**, *65*, 8391–8394; (d) Ley, S. V.; Thomas, A. W.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 669–671; (e) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977; (f) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945–7948; (g) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276.
2. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; (c) Meyer, S. D.; Schrieber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.
3. (a) For the first synthesis of IBX, see: Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727; (b) For a superior route to IBX, see: Friegerio, M.; Santagostino, M.; Supatore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538; (c) For use of IBX as a selective oxidant for alacohols, see: Refs. 1f and 1g.
4. (a) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2001**, *40*, 207–210; (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622–625; (c) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625–628; (d) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525–2529; (e) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597; (f) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183–3185.
5. (a) *Green Chemistry*, Chemical & Engineering News, **2001**, July 16, 27–34; (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic: London, 1998; (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035.
6. (a) The conversion of 3-iodophthalic acid, **8** to mIBX, **3** is carried out using $KBrO_3$ in 0.73 M H_2SO_4 at 55–60°C as follows: $KBrO_3$ (5 g, 30 mmol) was added in portions to a suspension of **8** (5 g, 17.1 mmol) in 70 mL of 0.73 M H_2SO_4 over a period of 20 min. The mixture was then maintained at 55–60°C for 12 h and the resulting clear orange solution was evaporated to yield an off-white solid, which was triturated with 30 mL of water at 0°C for 2 h and filtered to obtain a white solid. This was further triturated with hexanes (100 mL) for 6 h and filtered to give **3** (3.9 g, 71%) as a white solid, mp: 258–260°C; (b) no detonation of the sample was observed during the melting point determination of mIBX, **3**; (c) **3**: Mp 258–260°C; IR (KBr), 3503 3469, 3050, 1708, 1631, 1588, 1369, 730, 700 cm^{-1}; ^1H NMR (D_2O, 300 MHz): δ 8.35 (dd, $J=7.9$, 1.0 Hz, 1H), 8.09 (t, $J=7.9$ Hz, 1H), 7.94 (dd, $J=7.9$, 1.0 Hz, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 125.5, 127.5, 132.5, 134.7, 137.0, 147.1 (ring carbons), 168.9, 172.9 (carbonyl carbons)
7. Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485–3488.
8. A typical oxidation procedure in the mixed solvent system (oxidation of 4-nitrobenzyl alcohol, entry 5, Table 1, as an example) is as follows: To a solution of of 4-nitrobenzyl alcohol (100 mg, 0.65 mmol) in a mixture of water and THF (5 mL, 3:2 v/v) was added **3** (315 mg, 0.98 mmol). The homogeneous solution was left stirring at 55–60°C for 3 h and subsequently cooled and filtered to remove **12**. The filtrate after addition of H_2O (15 mL) was extracted with diethyl ether (2×10 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated to yield 79 mg of 4-nitrobenzaldehyde, identical in all respects with a commercial sample.
9. Compound **12**: Mp 261–262°C; IR (KBr), 3070, 2980, 1701, 1630, 1584, 1555, 1326, 820, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 8.24 (br s, 1H, D_2O exchangeable), 7.97–7.91 (m, 2H), 7.70 (dd, $J=6.9$, 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 121.8, 127.7, 127.9, 129.3, 134.9, 139.6 (ring carbons), 167.1, 169.3 (carbonyl carbons).